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| 09/353,423 | 07/15/1999 | TATTANAHALLI L. NAGABHUSHAN | CJ-0776QK | 3515 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/353,423 | NAGABHUSHAN ET AL. | |
| | Examiner | Art Unit | |
| | Anne-Marie Falk, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,19-34 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19-34 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed November 30, 2004 (hereinafter referred to as "the response") has been entered. Claims 1, 19, 30, and 34 have been amended. Claims 2-4 and 7-9 have been cancelled.

Accordingly, Claims 1, 19-34, and 36-39 remain pending in the instant application.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 30, 2004 has been entered.

At pages 6-8 of the response, Applicants argue that the specification provides an enabling disclosure for the compositions of Claims 19-33. The enablement rejection is withdrawn for Claims 19-29, but is maintained for Claims 30-33, directed to pharmaceutical compositions, for the reasons discussed herein below. As discussed in the first Office Action (mailed 10/4/00), the term "pharmaceutical" denotes an intended use (i.e., for therapy), but the disclosure is not enabling for the intended use (page 8, paragraph 3 of the Office Action mailed 10/4/00). When a composition claim recites an intended use, the specification must enable **that use.**

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 30-34 and 36-39 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-9 of the Office Action mailed 10/4/00, on pages 2-7 of the Office Action mailed 8/2/01, and on pages 2-5 of the Office Action mailed 7/29/03, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 9, paragraph 2 of the response, Applicants assert that the use of xenograft mice to determine whether a test compound is likely to be effective in other animals is widespread and dates back to at least Applicants' priority date. However, the issue is not whether xenograft models have been used for various purposes, but whether they are predictive in the gene therapy art, particularly in evaluating the biological effects of adenoviruses, and further in predicting anticancer therapeutics. The art cited in the prior Office Actions demonstrates that nude mouse models are not predictive of similar outcomes in immunocompetent animals, such as humans.

At page 9, paragraph 3 of the response, Applicants question what the difference is between artisans with an exceptionally high level of expertise and artisans with exceptional skill. Applicants assert that at the filing date there were many skilled practitioners capable of following protocols and performing the routine experimentation necessary to successfully practice Applicants' claimed methods. Applicants seem to be referring to the discussion at page 3 of the Office Action mailed 7/29/03, which pointed out that the practitioners that Applicant believes to be "one of ordinary skill in the art" which Applicant characterizes as "having at least an M.D. degree at a major university teaching hospital or prominent clinical institution" (page 6, paragraph 1 of the response filed 5/8/03). The difference is that it is rare that such individuals egage in routine experimentation to implement established gene therapy protocols, but rather are those individuals generally involved in ground-breaking research, and would not be considered one of ordinary skill in the art, but rather would be considered one of exceptional skill in the art. There is

a clear distinction between routine experimentation and undue experimentation, and those of exceptional skill in the art typically are involved in conducting the "undue experimentation" necessary to overcome problems in the art and develop successful gene therapy protocols.

At page 9, paragraph 3 of the response, Applicants point to Wills et al. (1994) and state that those skilled in the art were aware of this work and their ability to practice the necessary protocols is presumed. It appears that Applicants are asserting that those skilled in the art would be able to reproduce the experiments performed therein. However, the relevant issue is whether the skilled artisan could use routine experimentation to develop a successful gene therapy protocol to apply to an immunocompetent animal, such as a human, to achieve the same or similar result as obtained in the nude mouse. The cited art of record demonstrates that such animal models are not predictive of success in immunocompetent animals, particularly in the gene therapy art when repeat dosing of adenoviral vectors was relied upon to achieve the result obtained in the nude mouse experiments.

At page 10, paragraph 2 of the response, Applicants assert that adenoviral immune responses would not preclude the therapeutic use of the adenoviral vectors of the invention. No support is offered for this assertion. Applicants state that they have provided "a wealth of evidence" in their previous responses. The art to which Applicants seem to be referring has already been addressed in the prior Office Action (mailed 7/29/03) at page 4, paragraph 2. Applicants pointed to several articles published in 2002 and 2003, which discuss repeat dosing of adenoviral vectors. These are post-filing references which are not representative of the state of the art at the time the invention was made. As such, the skilled artisan would not have had the benefit of the additional teachings provided in these references.

At page 10, paragraph 10 of the response, Applicants rely on an unpublished article of Tsai et al. for reporting experiments performed by administering adenoviral vectors to animals with pre-existing adenoviral neutralizing antibodies. Applicants conclude that their nude mouse data are predictive. However, such a conclusion entirely ignores the cellular immune response that is known to occur upon re-

administration of adenoviral vectors. See the paragraph bridging pages 7-8 of the Office Action of 10/4/00, which points out the teachings of Verma et al. (1997) regarding the elicited cell-killing cellular response and Yang et al. (1996) who reports that the destruction of adenovirus-infected hepatocytes is due to CTL responses to both viral antigens and the transgene product. These articles are representative of the state of the art at the time of filing and demonstrate that the immune response to adenoviral vectors can be expected to have a pronounced effect on IFNα gene expression in an immunocompetent animal and that experiments performed in immunodeficient animals would therefore not be expected to be predictive of results obtainable in immunocompetent animals.

At page 11, paragraph 2 of the response, Applicants assert that even though no animal model is perfectly predictive of the human response, there is sufficient correlation of such models to the human condition for one of skill in the art to believe that an agent which demonstrates activity in such animal models will likely have activity in human beings. No support is offered for this assertion. Applicants seem to be arguing that any animal model data should be accepted as predictive of the human condition. This is not persuasive because, of prime importance, is that the animal model actually model the disease being studied, as well as the relevant conditions under which treatment must be conducted. In the instant case, the art shows that repeat dosing is problematic in the art of adenoviral gene therapy due to the immune response of immunocompetent animals, but the animal model relied upon is an immunodeficient animal in which repeat dosing is required to achieve an antitumor effect.

At page 12, paragraph 1 of the response, Applicants assert that the Examiner is relying on certain risks referred to in the Marshall (1995) article to reject the pending claims. It is unclear what Applicants are referring to because the Marshall article does not relate to risks, but rather discloses that expression studies conducted in animals were not predictive of the results that could be achieved in human patients. The article discloses that although researchers demonstrated expression of the CFTR gene in the surface

airway cells of laboratory animals, problems transferring sufficient quantities of the CFTR gene into patients' cells prevented the method from providing therapeutic benefit.

At page 12, paragraph 2 of the response, Applicants assert that there is a double-standard in the Patent Office. Applicants point to USPN 6,333,030 to Curiel. Applicants assert that the pending claims are of similar scope to those issued to Dr. Curiel in December 2001. First, each patent application is examined on the basis of its own merits, considering as a whole all the evidence presented. The specification itself need not be the sole source of the evidence presented. Second, it is noted that the example provided in the instant specification to evaluate the antitumor activity of an IFNα2b adenoviral vector relies on repeat dosing of the adenoviral vector to achieve the effect depicted in Figure 10.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

In the instant case, it is clear that further experimentation is required to allow the skilled artisan to practice the claimed invention and use the claimed compositions *in vivo* in an immunocompetent animal. Given that the state of the art is unpredictable, for reasons of record, the skilled artisan would have been required to engage in undue experimentation to practice the claimed invention *in vivo* and achieve the claimed result.

Given the limited working examples, the limited guidance in the specification, the broad scope of the claims with regard to the type of vector to be used, and the unpredictability of using the claimed methods and compositions *in vivo* to produce a therapeutic effect, undue experimentation would have been required for one skilled in the art to use the claimed compositions and practice the claimed methods *in vivo*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, Claim 1 recites the broad recitation of "an interferon-α polypeptide" in the body of the claim, and the claim also recites "an interferon-α2b polypeptide" in the preamble which is the narrower statement of the limitation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

Claim 19 is rejected under 35 U.S.C. 102(a) as being anticipated by Rutherford et al. (July 1996, J. of Interferon and Cytokine Research 16(7): 507-510).

Rutherford et al. (1996) disclose a recombinant vector for expressing an interferon-α polypeptide in a mammalian cell, wherein the nucleic acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence. The reference further discloses mouse L cells expressing non-secreted human interferon-α.

Thus, the claimed invention is disclosed in the prior art.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,069,133 (Chiou et al., priority to March 1996), Rutherford et al. (July 1996, J. of Interferon and Cytokine Research 16(7): 507-510), and Zhang et al. (April 1996, PNAS 93: 4513-4518).

Claims 20-29 are directed to recombinant vectors for expressing an interferon-a polypeptide, and particularly an interferon-α2b polypeptide, in a mammalian cell, wherein the vector comprises a nucleic acid segment encoding an interferon-α polypeptide lacking a secretion leader sequence. Claims 30-33 are directed to pharmaceutical formulations comprising a recombinant vector for expressing an interferon-α polypeptide in a mammalian cell, wherein the vector comprises a nucleic acid segment encoding an interferon-α polypeptide lacking a secretion leader sequence.

Chiou et al. disclose and claim a method of *in vivo* IFNα gene delivery to liver cells. The reference further discloses the desirability of delivering human IFN-α2b to liver cells (Column 3, Lines

30-46). The reference points out that IFN therapy holds particular promise in the treatment of chronic viral infections, such as hepatitis virus infections and that administration of exogenous IFN inhibits HBV and HCV infections (column 1, line 59 to column 2, line 3).

Zhang et al. (1996) disclose the *in vivo* administration of an adenovirus comprising the human consensus IFN gene.

Rutherford et al. (1996) disclose a recombinant vector for expressing an interferon-α polypeptide in a mammalian cell, wherein the nucleic acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence. The reference further discloses mouse L cells expressing non-secreted human interferon-α. The reference further discloses that the intracellular expression of interferon-α renders the cells less susceptible to encephalomyocarditis (EMC) virus infection. The antiviral effects are most likely mediated through activation of the transcription factor ISGF3, which occurs constitutively in cell lines expressing intracellular interferon.

Since Rutherford et al. disclose the antiviral activity of intracellular interferon and Zhang et al. disclose using an adenovirus to deliver the interferon gene to cells *in vivo*, one of skill in the art would have been motivated to prepare adenoviral vectors comprising an interferon-α gene lacking the secretion leader sequence so that the vectors could be used for *in vivo* delivery of the gene which would then drive expression of intracellular interferon-α in cells. Since Chiou et al. disclose that interferon-α, and particularly IFN-α2b, are useful for their antiviral activity and are particularly useful for delivery to liver cells for the treatment of HBV, one of skill in the art would have been motivated to use a liver-specific promoter to drive expression of an intracellular form of IFNα, particularly IFN-α2b, in the liver to test its antiviral activity against HBV. One of skill in the art would have anticipated a reasonable expectation of success because only standard molecular biology techniques are required to make the adenoviral vector construct and methods for assaying for the presence of HBV are known in the art, as disclosed by Chiou

et al. Therefore it would have been obvious to one of skill in the art at the time of the invention to have prepared the claimed recombinant vectors and use them for *in vivo* expression of IFN-α2b in liver cells.

One would have been motivated to have combined the teachings of Chiou et al., Zhang et al., and Rutherford et al. in order to to test the antiviral activity of a vector encoding intracellular IFN-α2b against HBV.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

*Conclusion*

No claims are allowed.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER